

**AMENDMENTS TO THE CLAIMS**

1. (Currently Amended) A modified release oral dosage form tablet comprising (a) particles comprising (i) a solid carrier and (ii) tacrolimus dispersed in a vehicle ~~tacrolimus dispersed in a vehicle~~, and (b) a modifying release agent, wherein
  - (i) the vehicle comprises polyethylene glycol having an average molecular weight of ~~at least~~ 1500 to 35000 and a poloxamer, and
  - (ii) less than 20% w/w of the tacrolimus is released within 0.5 hours, when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium, and
  - (iii) the particles have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 1000  $\mu\text{m}$ .
2. (Currently Amended) The modified release oral dosage form tablet according to claim 1, wherein less than 20% w/w of the tacrolimus is released within 3 hours.
3. (Currently Amended) The modified release oral dosage form tablet according to claim 1, wherein less than 10% w/w of the tacrolimus is released within 3 hours.
4. (Currently Amended) The modified release oral dosage form tablet according to claim 1, wherein at least 50 % w/w of the tacrolimus is released within 4 hours when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium during the first 2 hours and then using a dissolution medium having a pH of 6.8.
5. (Currently Amended) The modified release oral dosage form tablet according to claim 1, wherein at least 50 % w/w of the tacrolimus is released within 2.5 hours when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium during the first 2 hours and then using a dissolution medium having a pH of 6.8.
6. (Currently Amended) The modified release oral dosage form tablet according to claim 1, wherein less than 50 w/w% of the tacrolimus is released within 8 hours, ~~preferably within 15 hours~~, when subjected to an *in vitro* dissolution test using USP Paddle method and an aqueous dissolution medium adjusted to pH 4.5 with 0.005% hydroxypropylcellulose.

7. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 6, wherein less than 40 w/w% of the tacrolimus is released within 8 hours, ~~preferably within 15 hours.~~
8. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, which is designed to substantially avoid CYP3A4 metabolism in the gastrointestinal tract upon oral administration.
9. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 8, wherein the composition is coated with an enteric coating.
- 10-19. (Canceled)
20. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, wherein the ~~mixtures comprises a~~ polyethylene glycol and [[a]] poloxamer are in a proportion by weight of between 1: 3 and 10: 1.
21. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, wherein the poloxamer is poloxamer 188.
22. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, wherein the polyethylene glycol has an average molecular weight of about 6000 (PEG6000).
23. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, wherein the ~~which further comprises one or more~~ modifying release agent ~~agents~~ is selected from the group consisting of water-miscible polymers, water-insoluble polymers, oils, ~~and~~ oily materials, and mixtures thereof.
24. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 23, wherein the water-insoluble polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof.
25. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 23, wherein the oil or oily material is hydrophilic and selected from the group consisting of polyether

glycols such as polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers; polyglycolized glycerides, and mixtures thereof.

26. (Canceled)

27. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 23, wherein the oil or oily material is hydrophobic and selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

28. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 23, wherein the oil or oily hydrophobic material has a melting point of at least about 20°C.

29. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 23, wherein the water-miscible polymer is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly-s-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA, polymethacrylic polymers and polyvinyl alcohol (PVA), poly (ethylene oxide) (PED) and mixtures thereof.

30. (Canceled)

31. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, which is entero-coated using a water-miscible polymer having a pH-dependant solubility in water.

32. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 31, wherein the water-miscible polymer is selected from the group consisting of polyacrylamides; phthalate derivatives such as acid phthalate of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; phthalate of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers; polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymers; styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and mixtures thereof.

33. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, which further comprises one or more pharmaceutical acceptable excipients.

34. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 33, wherein the pharmaceutically acceptable excipients are selected from the group consisting of fillers, diluents, disintegrants, binders and lubricants.

35. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim ~~33~~ 1, wherein the particles are ~~tablet comprises~~ compressed particles.

36. (Canceled)

37. (Currently Amended) A modified release tablet providing extended release of tacrolimus, comprising a compressed mixture of (A) particles comprising of (i) a solid carrier and (ii)

tacrolimus dispersed in a vehicle comprising (a) polyethylene glycol having an average molecular weight of 1500 to 35000 and (b) a poloxamer, and (ii) carrier particles and (B) one or more modifying release agents, one or more pharmaceutically acceptable excipients, wherein (1) the vehicle comprises polyethylene glycol having an average molecular weight of at least 1500 and a poloxamer, (ii) wherein

less than 20% w/w of the tacrolimus is released within 0.5 hours, when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium, and

~~(iii)~~ the particles, before compression, have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about ~~300~~ 1000  $\mu\text{m}$ .

38–39. (Canceled)

40. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 1, which further comprises a pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents and absorption enhancing agents.

41. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 33, wherein at least one pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

42. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 41, wherein at least one pharmaceutical acceptable excipient is a silica acid or a derivative or salt thereof.

43. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 41, wherein at least one pharmaceutically acceptable excipient is silicon dioxide or a polymer thereof.

44. (Currently Amended) The modified release oral dosage form ~~tablet~~ according to claim 43, wherein the silicon dioxide comprises colloidal silica.

45–52. (Canceled)

53. (New) The modified release oral dosage form according to claim 1, wherein the particles have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 400  $\mu\text{m}$ .

54. (New) The modified release oral dosage form according to claim 1, wherein the solid carrier is lactose.

55. (New) The modified release tablet according to claim 37, wherein the particles have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 400  $\mu\text{m}$ .

56. (New) The modified release oral dosage form according to claim 37, wherein the solid carrier is lactose.

57. (New) A modified release oral dosage form comprising  
(a) solid carrier particles sprayed with tacrolimus dispersed in a vehicle of (i) polyethylene glycol having an average molecular weight of 1500 to 35000 and (ii) a poloxamer, the sprayed particles having a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 1000  $\mu\text{m}$ , and  
(b) a modifying release agent,

wherein less than 20% w/w of the tacrolimus is released within 0.5 hours, when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium.

58. (New) The modified release oral dosage form according to claim 57, wherein the particles have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 400  $\mu\text{m}$ .

59. (New) The modified release oral dosage form according to claim 57, wherein the dosage form comprises from about 10 to about 50% polyethylene glycol, and the weight ratio of polyethylene glycol to poloxamer is between 1:3 and 10:1.

60. (New) A once-daily modified release tacrolimus tablet prepared by:

- (a) dissolving tacrolimus in a liquid mixture of polyethylene glycol having an average molecular weight of 1500 to 35000 and a poloxamer at a temperature below the melting point of tacrolimus;
- (b) spraying the liquid mixture onto solid carrier particles to form a free-flowing powder have a geometric weight mean diameter  $d_{gw}$  of from about 50 to about 1000  $\mu\text{m}$ ;
- (c) adding a modifying release agent to the powder; and
- (d) compressing the powder to form a tablet,

wherein

- (i) the tablet comprises from about 10 to about 50% polyethylene glycol,
- (ii) the weight ratio of polyethylene glycol to poloxamer is between 1:3 and 10:1, and
- (iii) the tablet releases less than 20% w/w of the tacrolimus within 0.5 hours, when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium.

61. (New) The modified release tablet according to claim 60, wherein the particles have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 400  $\mu\text{m}$ .

62. (New) An oral dosage form providing extended release of tacrolimus prepared from (a) particles comprising (i) a solid carrier and (ii) tacrolimus dispersed in a vehicle, and (b) a modifying release agent, wherein

- (i) the vehicle comprises polyethylene glycol having an average molecular weight of 1500 to 35000 and a poloxamer, wherein the amount of polyethylene glycol is from about 10% to about 50%, based upon the total weight of the oral dosage form,
- (ii) less than 20% w/w of the tacrolimus is released within 0.5 hours, when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium, and
- (iii) the particles have a geometric weight mean diameter  $d_{gw}$  of from about 50  $\mu\text{m}$  to about 1000  $\mu\text{m}$ .